AUG 25 1998

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 97-505

LINCOMIX® 10/20/50 Feed Medications

(Lincomycin Hydrochloride)

Sponsored by:

Pharmacia and Upjohn Animal Health.
7000 Portage Road
Kalamazoo, Michigan 49001

AUG 25 1998

Date of Approval: _____

NADA 97-505

FOIS 1

1. GENERAL INFORMATION

NADA NUMBER:	97-505
SPONSOR:	Pharmacia and Upjohn Animal Health 7000 Portage Road Kalamazoo, Michigan 49001
ACCEPTED DRUG NAME:	lincomycin hydrochloride
TRADE NAME:	LINCOMIX® 10/20/50 Feed Medications
MARKETING STATUS:	Over-the-counter
EFFECT OF SUPPLEMENT:	This supplemental approval provides for the assignment of a tolerance of 0.6 ppm for lincomycin in swine liver, a tolerance of 0.1 ppm for lincomycin in swine muscle, and the assignment of an Acceptable Daily Intake (ADI) of 25 micrograms per kilograms per body weight per day for the total residues of lincomycin. In addition, this supplement reduces the slaughter period for feed uses of lincomycin in swine from 6 days to O days.

II. INDICATIONS FOR USE

Swine--For treatment of swine dysentery. For treatment and control of swine dysentery. For reduction of severity of mycoplasmal pneumonia. For increase in rate of gain in growing-finishing swine.

Broiler chickens--For increase of rate of weight gain and feed efficiency. For the control of necrotic enteritis.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

As discussed in the Freedom of Information(FOI) Summary for the original approval of NADA 97-505 dated February 25, 1976.

IV. HUMAN SAFETY

A. Toxicity Studies

Toxicity studies conducted for lincomycin were described in the FOI Summary for NADA 97-505 of June 1, 1990.

An ADI of 1.5 mg per 60 kg person per day (equivalent to 0.025 mg/kg body weight per day) was assigned based on procedures described in the *Guideline for Establishing a Safe Concentration* (FR 37499-37500, July 22, 1994) and the CVM document, *Guidance: Microbiological Testing of Antimicrobial Drug Residues in Food* (FDA/CVM, January 1996).

B. Calculations of Safe Concentrations (SC):

Based on the procedures described in the CVM document *Guideline for Establishing a Safe Concentration* dated July 1994, safe concentrations of total residues of lincomycin may be calculated:

$$\text{Safe Concentration (SC)} = \frac{\text{Acceptable Daily Intake (ADI)}}{\text{Consumption Value}}$$

The daily consumption values of edible tissues are approximated as 300 g (0.3 kg) for muscle, 100 g (0.1 kg) for liver, 50 g (0.05 kg) for fat/skin, and 50 g (0.05 kg) for kidney.

$$\text{SC (muscle)} = \frac{1.5 \text{ mg/day}}{0.3 \text{ kg/day}} = 5 \text{ mg/kg} = 5 \text{ ppm in muscle}$$

$$\text{SC (liver)} = \frac{1.5 \text{ mg/day}}{0.1 \text{ kg/day}} = 15 \text{ mg/kg} = 15 \text{ ppm in liver}$$

$$\text{SC (fat/skin)} = \frac{1.5 \text{ mg/day}}{0.05 \text{ kg/day}} = 30 \text{ mg/kg} = 30 \text{ ppm in fat/skin}$$

$$\text{SC (kidney)} = \frac{1.5 \text{ mg/day}}{0.05 \text{ kg/day}} = 30 \text{ mg/kg} = 30 \text{ ppm in kidney}$$

c. Determination of Tolerances

Based on data from studies described in the 1998 FOI Summary for NADA 34-025, a tolerance of 0.6 part per million is established for parent lincomycin (marker residue) in the liver (target tissue) of swine. In addition, FDA is retaining the currently codified tolerance of 0.1 ppm for lincomycin in muscle.

D. Withdrawal Times

1. Determination of the Residue Decline of Lincomycin in the Liver of Swine Treated with Lincomycin Hydrochloride (U-10149A) at 40, 100, or 200 grams of Lincomycin Freebase Equivalents per Ton of Feed

a. Report Number: 768-7926-95-003

b. Study Completion: February 13, 1996

c. Investigator: J.L. Nappier
Pharmacia & Upjohn Company
Kalamazoo, MI 49001

d. Substance and Dosage Form: Lincomycin was provided in feed.

e. Species and Strain of Animal: Yorkshire-Hampshire cross swine.

f. Number of Animals per Group: Two pigs of each sex per dose per time point (64 total).

g. Levels and Duration of Dosing: Diets were fed for 7 days.

h. Route of Administration: Orally, via feed.

i. Parameters: Study parameters included assay of parent lincomycin residues in the liver and kidneys of swine at various times after the withdrawal of medicated feed. Residue levels were determined by a gas chromatographic method with mass spectrometric detection.

j. Results:

Table 1. Mean levels of parent lincomycin in the livers of swine (ppm) following administration of LINCOMIX® in feed for 7 clays

Treatment	O hr	1 hr	3 hr	6 hr	12hr	24 hr	48 hr
Control	<0.02	-a	-				
40 g/ton	-	0.07	0.06	0.04	0.02	<0.02	-
100 g/ton	-		0.12	0.07	0.04	<0.02	<0.02
200 #ton	-		0.27	0.17	0.08	0.04	<0.02

a. - samples were not taken at that dose/time point

Mean residue levels were found to be below the tolerance at all time points, even the 200 g/ton level at 3 hours after the final dose.

2. Calculation of Withdrawal Times

Applying its statistical method for determining withdrawal periods to the data sets for lincomycin at 40, 100, and 200 g/ton, FDA found that the 99°/0 tolerance limit, with 95% confidence, would be below 0.6 ppm at 1 hour, 1 hour and 8 hours, respectively. Each of those statistically derived times permits the assignment of a O-day withdrawal period for swine treated with feed containing up to 200 g/ton lincomycin.

E. Regulatory Method:

Refer to the FOI Summary for NADA 97-505 dated February 25, 1976, for information regarding the regulatory method.

V. AGENCY CONCLUSIONS

Based on the revised consumption values provided in the *Guideline for Establishing a Safe Concentration* (FR 37499-37500, July 22, 1994) and the CVM document, *Guidance: Microbiological Testing of Antimicrobial Drug Residues in Food* (FDA/CVM, January 1996), the Center has established new safe concentrations and tolerances for total residues in edible tissues. The acceptable daily intake (ADI) (25 micrograms per kilogram of body weight per day) and the marker residue tolerance of 0.6 ppm for lincomycin in swine liver (target tissue) will be codified under 21 CFR 556.360. In addition, the currently codified tolerance of 0.1 ppm will be retained for lincomycin in swine muscle.

In addition, the slaughter withdrawal period for feed uses of lincomycin in swine has been reduced from 6 days to O days. The LIMITATIONS section in 21 CFR 558.325 will be amended to reflect the zero-day withdrawal period.

According to 21 CFR 514. 10f and (xi), this is a Category II supplement. The approval of this change required a re-evaluation of the slaughter withdrawal period and the tolerance according to current food safety guidance, but did not require a reevaluation of target animal safety or effectiveness data in the parent application.

The agency has determined under 21 CFR 25.33 (a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

LINCOMIX® 10/20/50 Feed Medications are not currently under any unexpired U.S. patents.

VI. APPROVED PRODUCT LABELING

A copy of the draft facsimile labeling is attached to this document.

A. LINCOMIX® 50 Type A Medicated Article Bag Label

B. LINCOMIX® 20 Type A Medicated Article Bag Label

C. LINCOMIX® 10 Type B Medicated Feed Bag Label

NDC 0009-0494-17

LINCOMIX® 20

Feed Medication
(Type A Medicated Article)
20 grams/lb

For increase in rate of weight gain, for improved feed efficiency, and for the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to lincomycin in broilers.

For the treatment and control of swine dysentery

For reduction in the severity of swine mycoplasmal pneumonia caused by *Mycoplasma hyopneumoniae*

For increase in rate of weight gain in growing-finishing swine.

Active Drug Ingredient

Each pound contains:

Lincomycin ..... 20 grams
(as lincomycin hydrochloride agricultural grade)

Inactive Ingredients

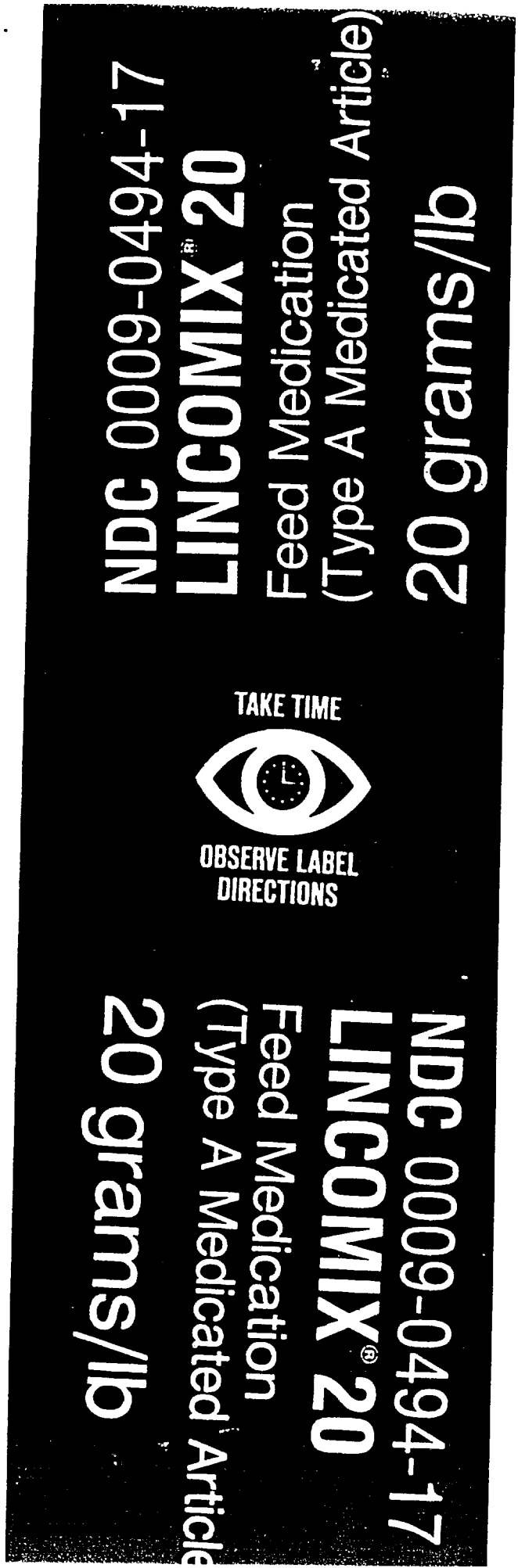
Soybean hulls, #20 grind; mineral oil, USP.

IMPORTANT:
Must be thoroughly mixed in feeds before use.
Store opened bag in dry place to prevent caking.
Store at room temperature.

NET WEIGHT 50 Lb (22.6 kg)

Upjohn

The Upjohn Company
Kalamazoo, MI 49001, USA



Proof of Purchase-Seal
Lincomix 20 (50 lb)
N 3 0009-0494-17 9

LINCOMIY'20
Feed Medication
(Type A Medicated Article)

20 grams/lb

Broilers
For increase in rate of weight gain, for improved feed efficiency and for the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to lincomycin in broilers.

DIRECTIONS FOR USE

For Increase in Rate of Weight Gain and Improved Feed Efficiency:
LINCOMIX 20, 20 grams/lb, should be mixed into the complete feed supplied to broiler chickens so that the final feed contains 2 to 4 grams of lincomycin per ton of feed.

For the Control of Necrotic Enteritis:
LINCOMIX 20, 20 grams/lb, should be mixed into the complete feed supplied to broiler chickens so that the final feed contains 2 grams of lincomycin per ton of feed.

MIXING DIRECTIONS

Intermediate Premix Amount of LINCOMIX 20 per 1000 lb (454 kg) of Feed Ingredients	*Complete Feed* Amount of Intermediate Premix to use to Provide Desired Grams of lincomycin per ton of Type C Medicated Feed		
	lincomycin per ton of feed		
	2 grams	*3 grams*	*4 grams*
50 lbs	2 lbs	3 lbs	4 lbs
10 lbs	10 lbs	15 lbs	20 lbs
5 lbs	20 lbs	30 lbs	40 lbs

WARNING
When LINCOMIX 20 is used in approved combinations with other drugs, follow the required withdrawal times for those drugs. No drug withdrawal period is required before slaughter of birds fed LINCOMIX 20 at approved concentrations (2 to 4 grams lincomycin per ton of feed).

CAUTION: Not for use in layers, breeders, or turkeys. (For additional Cautions, see below.)

SWINE
For the Treatment and Control of Swine Dysentery. For Reduction in the Severity of Swine Mycoplasmal Pneumonia caused by *Mycoplasma hyopneumoniae.* For increase in rate of weight gain in growing-finishing swine.

DIRECTIKINS FOR USE

For Treatment of Swine Dysentery:
Feed 100 grams of lincomycin per ton of complete feed as the sole ration for three weeks or until signs of disease (watery, mucoid, or bloody stools) disappear.

For Treatment and Control of Swine Dysentery:
Feed 100 grams of lincomycin per ton of complete feed as the sole ration for three weeks or until signs of disease (watery, mucoid, or bloody stools) disappear, followed by 40 grams of lincomycin per ton.

For Control of Swine Dysentery:
Feed 40 grams of lincomycin per ton of complete feed as the sole ration. For use in animals or on premises with a history of swine dysentery but where symptoms have not yet occurred.

For Reduction in the Severity of Swine Mycoplasmal Pneumonia:
Feed 200 grams of lincomycin per ton of complete feed as the sole ration for 21 days.

For Increase in Rate of Weight Gain in Growing-Finishing Swine:
Feed 20 grams of lincomycin per ton of complete feed as the sole ration from weaning to market weight.

MIXING DIRECTIONS

Type C Medicated Feeds

For Treatment of Swine Dysentery:
To make complete feed containing 100 grams of lincomycin, add 5 lbs of LINCOMIX 20 per ton.

For Control of Swine Dysentery:
To make complete feed containing 40 grams of lincomycin, add 2 lbs of LINCOMIX 20 per ton.

For Reduction in the Severity of Mycoplasmal Pneumonia:
To make complete feed containing 200 grams of lincomycin, add 10 lbs of LINCOMIX 20 per ton.

For Increase in Rate of Weight Gain in Growing-Finishing Swine:
To make complete feed containing 20 grams of lincomycin, add 1 pound of LINCOMIX 20 per ton.

WARNING
~~DO NOT SLAUGHTER SWINE FOR HUMAN CONSUMPTION FOR 6 DAYS FOLLOWING LAST TREATMENT WHEN FED AT 100 OR 200 G/TON COMPLETE FEED~~
~~NOT FOR HUMAN USE~~

CAUTION: Occasionally, swine fed lincomycin may within the first two days after the onset of treatment develop diarrhea and/or swelling of the anus. On rare occasions, some pigs may show reddening of the skin and irritable behavior. These conditions have been self-correcting within five to eight days without discontinuing the lincomycin treatment. Not to be fed to swine that weigh more than 250 pounds.

Do not allow rabbits, hamsters, guinea pigs, horses, or ruminants access to feeds containing lincomycin. Ingestion by these species may result in severe gastrointestinal effects.

Good Manufacturing Practices Should Be Observed in Preparing Feeds Containing LINCOMIX 20.
This includes appropriate clean-out procedures to avoid cross-contamination.

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Restricted Drug—Use Only as Directed (California)

The Upjohn Company • Kalamazoo, MI 49001, USA

When LINCOMIX is used in approved combinations with other drugs, follow the required withdrawal times for those drugs. No drug withdrawal period is required before slaughter of swine fed LINCOMIX at approved concentrations (20, 40, 100 or 200 ---- lincomycin

NDC 0009-0494-17
LINCOMIX® 20
Feed Medication
(Type A Medicated Article)
20 grams/lb

TAKE TIME

OBSERVE LABEL DIRECTIONS

NDC 0009-0494-17
LINCOMIX® 20
Feed Medication
(Type A Medicated Article)
20 grams/lb

Proof of Purchase Seal
Lincomix 50 (50 lb)

NDC 0009-0487-05

LINCOMIX® 50

Feed Medication
(Type A Medicated Article)

50 grams/lb

For increase in rate of weight gain, for improved feed efficiency, and for the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to lincomycin in broilers.

For the treatment and control of swine dysentery

For reduction in the severity of swine mycoplasmal pneumonia caused by *Mycoplasma hyopneumoniae*

For increase in rate of weight gain in growing-finishing swine.

Each pound contains:

Active Drug Ingredient

Lincomycin . . . . . (as lincomycin hydrochloride agricultural grade) 50 grams

Inactive Ingredients

Soybean hulls, #20 grind; Mineral Oil, USP

IMPORTANT:

Must be thoroughly mixed in feeds before use.

Store opened bag in dry place to prevent caking.

Store at room temperature.

NET WEIGHT 50 Lb (22.6 kg)

Upjohn

The Upjohn Company • Kalamazoo, MI 49001, USA

NDC 0009-0487-05
LINCOMIX® 50
Feed Medication
(Type A Medicated Article)
50 grams/lb

TAKE TIME

OBSERVE LABEL DIRECTIONS

NDC 0009-0487-05
LINCOMIX® 50
Feed Medication
(Type A Medicated Article)
50 grams/lb

i'iIVCOMIr'50
Feed Medication
(Type A Medicated **Article)**
50 grams/lb

Broilers
For increase in rate of weight gain, for improved feed efficiency and for the control of necrotic enteritis caused or complicated by *Clostridium spp. or* other organisms susceptible to lincomycin in broilers.

DIRECTIONS FOR USE
Far **Increase la Rate of Weight Gain and Improved Feed Efficiency:**
LINCOMIX 50, 50 grams/lb. should be mixed into the complete feed supplied to broiler chickens so that the final feed contains 2 to 4 grams of lincomycin per ton of feed.
For the Control of Necrotic Enteritis:
LINCOMIX 50, 50 grams/lb, should be mixed into the complete feed supplied la broiler chickens so that the final feed contains 2 grams of lincomycin per ton of feed.

MIXING DIRECTIONS

Intermediate Premix Amount of LINCOMIX 50 per fOOO lb (454 kg) of Feed Ingredients	*Complete Feed* Amount of Intermediate emixbotgse la Provide Desired Grams of lincomycin per ton of Type C Medicated Feed *lincomycin per ton of feed*		
	2 grams	*3 grams*	*4 grams*
20 lbs	2 lbs	3 lbs	4 lbs
4 lbs	10 lbs	15 lbs	20 lbs
2 lbs	20 lbs	30 lbs	40 lbs

WARNING
When LINCOMIX 50 Is used In approved combinations with other drugs, follow the required withdrawal times for those dregs. No drug withdrawal period is required before slaughter of birds fed LINCOMIX 50 at approved concentrations (2 to 4 grams lincomycin per ton of feed).

CAUTION: Not for use in layer% breeders, or turkeys. (For Additional Cautions, See Below)

sWINE
For the Treatment and Control of Swine Dysentery. For Reduction In the Severity of Swine Mycoplasmal Pneumonia caused by *Mycoplasma hyopneumoniae*. For increase in rate of weight gain in growing-finishing swine.

DIRECTIONS FOR USE
Far **Treatment** al **Swine Dysentery:**
Feed 100 grams of lincomycin par too of complete feed as the sole ration for three weeks or until signs of disease (watery, mucoid, or bloody stools) disappear.

For Treatment and Control of Swine Dysentery:
Feed 100 grams of lincomycin per ton of complete feed as the sole ration for three weeks or until signs of disease (watery, mucoid, or bloody stools) disappear, followed by 40 grams of lincomycin per ton.

For Control of Swine Dysentery:
Feed 40 grams of lincomycin ptrf ton of complete feed as the sole ration. For use in animals or on premises with a history of swine dysentery but where symptoms have not yet occurred.

For Reduction In the Severity of Swine Mycoplasmal al Pneumonia:
Feed 200 grams of lincomycin per ton of complete feed as the sole ration for 21 days.

For Increase la Rate of Weight Gain la Growing-Finishing Swine:
Feed 20 grams of lincomycin per ton of complete feed as the sole rattan from weaning to market weight

MIXING DIRECTIONS

Type C Medicated Feeds:

For **Treatment** of **Swine Dysentery:**
To make complete feed containing 100 grams of lincomycin, add 2 lbs of LINCOMIX SO per ton.

For Control of Swine Dysentery:
To make complete feed containing 40 grams of lincomycin, add 0.8 lbs of LINCOMIX 50 per ton.

For Reduction In the Severity of Mycoplasmal Pneumonia:
To make complete feed containing 200 grams of lincomycin, add 4 lbs of LINCOMIX 50 per ton.

For Increase la Rate of Weight Gain la Growing-Finishing Swine:
To make complete feed containing 20 grams of lincomycin per ton utilize the directions fisted below.

Far **Control of Swine Dysentery:**
To make complete feed containing 40 grams of lincomycin per ton utilize the directions fisted below.

MIXING DIRECTIONS

Intermediate Premix Amount of LINCOMIX 50 per 1000 lb (454 kg] of Feed Ingredients	Complete Feed Amount of Intermediate Premix to use to Provide Desired Grams of lincomycin per ton of feed lincomycin oar ton of feed	
	20 grams	40 grams
50 lbs	8 lbs	16 lbs
40 lbs	10 fbs	20 lbs
20 lbs	20 lbs	40 fbs

WARNING
~~DO NOT SLAUGHTER SWINE FOR HUMAN CONSUMPTION FOR 6 DAYS FOLLOWING LAST TREATMENT WHEN FED AT 100 OR 200 G/TON OF COMPLETE FEED~~
~~NOT FOR HUMAN USE~~

CAUTION
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Do not allow rabbits. hamsters. guinea pigs, horses, or ruminants access to feeds containing lincomycin. Ingestion by these species may result in severe gastrointestinal effects.

Good Manufacturing Practices Should Be Observed in Preparing Feeds Containing LINCOMIX SO.
This Includes Appropriate Clean-out Procedures to Avoid Cross Contamination.

810731614 **Restricted Drug—Use Only as Directed (California)**

The **Upjohn Company** • Kalamazoo, MI 49001, USA

When LINCOMIX is used In approved combinations **with other** drugs, follow the required withdrawal *times* for those drugs. No drug withdrawal period Is required before slaughter of swine fed LINCOMIX at *approved* concentrations (20, 40. 100 or ZOO grams lincomycin per ton of feed).